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Mechanism of action of anticandidal dipeptides containing inhibitors of glucosamine-6-phosphate synthase.

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Abstract

The mechanism of anticandidal action of novel synthetic dipeptides containing N3-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP) residues was shown to be consistent with the "warhead delivery" concept. FMDP dipeptides were shown to be transported into Candida albicans cells by the di-tripeptide permease and subsequently hydrolyzed by intracellular peptidases, especially aminopeptidase. The anticandidal activity of the particular FMDP dipeptide was influenced by the rate of its transport and, to a lower extent, by the intracellular cleavage rate. A high transport rate accompanied by a high cleavage rate resulted in the high anticandidal activity of L-norvalyl-FMDP. The strong growth-inhibitory effect of this compound was the consequence of inhibition of the enzyme glucosamine-6-phosphate synthase by the released FMDP. The action of L-norvalyl-FMDP on exponentially growing C. albicans cells resulted in a sharp decrease of incorporation of 14C label from [14C]glucose into chitin, mannoprotein, and glucan. This effect, as well as the growth-inhibitory effect, was fully reversed by exogenous N-acetyl-D-glucosamine. Glucosamine-6-phosphate synthase was proved to be the only essential target for FMDP dipeptides. Scanning electron microscopy of C. albicans cells treated with L-norvalyl-FMDP revealed highly distorted, wrinkled, and collapsed forms. Cells formed long, bulbous chains, and partial lysis occurred.

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